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High-Dose Cytarabine-Containing Chemotherapy With or Without Granulocyte Colony-Stimulating Factor for Children With Acute Leukemia

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We sought to determine the role of granulocyte colony-stimulating factor (G-CSF) as an adjunct therapy in high-dose cytarabine-containing chemotherapy (HD C/T) for children with acute leukemia. Seventeen patients, aged 9 months to 18 years old, 8 ALL and 9 AML, were treated with cytarabine (Ara-C) 1 g/m^2 q12h for 8 doses with mitoxantrone, idarubicin, VP-16, or asparaginase. A total of 71 courses of HD C/T was given. G-CSF was not used in 14 courses (Group A). Prophylactic G-CSF was given in 57 courses (Group B) as 200 μg/m^2/d SC started one day after the completion of HD C/T and continued until the neutrophil recovery was maintained. The incidences of sepsis per course in Group A and Group B were 35.7% (5/14) and 40.4% (23/57), respectively. While 2 patients in Group A died of sepsis or pneumonia, none in Group B died. The mortality and delay in chemotherapy were fewer in Group B (P = 0.037 and 0.0006, respectively, Fisher exact test). There was a shorter average number of days of neutrophil <500/cumm, antibiotic usage, fever, and hospital stay in Group B (11, 8, 5, 17 days in Group B vs. 21, 17, 10, 37 days in Group A; P = 0.0001, log-rank test; 0.0006, 0.0023, 0.0001, Wilcoxon rank sum test, respectively). The incidence of neutropenic fever was lower in Group B, but the difference did not reach statistical significance (P = 0.06, Fisher exact test). We conclude that G-CSF as an adjunct therapy in HD C/T is effective in reducing mortality, days of neutropenia, antibiotic usage, fever, hospital stay, and frequency of delay in chemotherapy. The efficacy of this treatment approach requires further testing in a randomized, controlled trial. Am. J. Hematol. 58:20–23, 1998. © 1998 Wiley-Liss, Inc.

Key words: G-CSF; HD C/T; acute leukemia

INTRODUCTION

In relapsed or refractory acute lymphoblastic leukemia and acute myeloid leukemia, high-dose cytarabine-containing chemotherapy (HD C/T) has produced good remission rates and high long-term disease-free survival rates [1–6]. However, the myelotoxicity of these treatment modalities results in a substantial morbidity related primarily to infectious complications, which are mainly determined by the degree and duration of neutropenia. This results in frequent delays in the scheduled administration of chemotherapeutic agents, despite aggressive supportive therapy. It is apparent that such inadvertent treatment delays may adversely affect treatment outcome.

In recent clinical trials, the use of granulocyte colony-stimulating factor (G-CSF) after intensive chemotherapy has been associated with reductions in the severity and duration of myelosuppression, morbidity, and mortality from myelosuppression-related complications [7–12]. In addition, the incidences of treatment delays decreased [12,13].

In this study, we sought to determine the role of G-CSF as an adjunct in HD C/T for children with acute leukemia.

PATIENTS AND METHODS

Patients

From November 1991 to December 1996, 17 patients with acute leukemia were enrolled. There were 14 males and 3 females whose ages ranged from 9 months to 18 years old. The status of leukemia included de novo AML in 6 patients, relapsed AML in 2, AML transformed from

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TABLE I. Characteristics of the Patients Not Receiving Granulocyte Colony-Stimulating Factor*

No.	Leukemia	Status	Chemotherapy	No. of HD C/T for reinduction	No. of HD C/T for consolidation
1	ALL	3rd relapse	HD Ara-C + Mito	1	
		4th CR	HD Ara-C + Mito		2

*ALL: acute lymphoblastic leukemia; CR: in complete remission; HD C/T: high-dose cytarabine containing chemotherapy; HD: high-dose; Ara-C: cytarabine; Mito: mitoxantrone.

CML in 1, refractory ALL in 1, and relapsed ALL in 7. A total of 71 courses of HD C/T was given. Each patient received at least one course of chemotherapy, and up to a maximum of 14 courses. HD C/T was principally repeated every 4 weeks. All patients received cytarabine (Ara-C) 1 g/m^2 q12h for 8 doses in combination with another chemotherapeutic agent. Cytarabine plus mitoxantrone 10 mg/m^2/day for 4 days was used in 17 courses, cytarabine plus idarubicin 5 mg/m^2/day for 5 days in 11 courses, cytarabine plus etoposide 100 mg/m^2/day for 5 days in 34 courses, and cytarabine plus L-asparaginase 6,000 U/m^2/day for 5 days in 9 courses. G-CSF was not used in 14 courses of HD C/T (Group A), since the parental consent was not obtained. Prophylactic G-CSF was given in 57 courses (Group B). Four patients participated in both groups. Six patients with de novo AML received a total of 22 courses of HD C/T in Group B, the other patients (in both groups) were of poor-risk or relapsed acute leukemia. The 17 patients were then divided into groups of (1) no G-CSF, 1 patient; (2) G-CSF, 12 patients; and (3) intermittent G-CSF, 4 patients. The characteristics of these patients are shown in Tables I–III.

Study Design and Statistical Analysis

G-CSF (Filgrastim, Kirin Brewery, Japan) was given as a single daily subcutaneous injection at a dose of 200 μg/m^2/day, starting on the next day after the completion of chemotherapy. The administration of G-CSF was continued until the absolute neutrophil count (ANC) exceeded 1,500/cumm. After reaching this level, the dose was reduced to 100 μg/m^2/day, then to 50 μg/m^2/day and treatment was finally discontinued if the ANC stayed above 1,500/cumm. During this study, hemoglobin and platelet count were checked twice a week and white blood count with differential count was checked daily. Fever was defined as axillary temperature above 38.5°C once or above 38°C twice within 6 h. Neutropenic fever was defined as fever with ANC of patient below 1,000/cumm. Sepsis was defined as at least one positive blood culture with a significant bacterial pathogen in association with appropriate signs and symptoms of a systemic infection. Patients who died before their ANC reach 500/cumm were regarded as having had no recovery during the treatment period. It was considered a chemotherapy delay if the next course of chemotherapy was postponed for more than one week. We used the Fisher exact test to compare the incidences of mortality, sepsis, neutropenic fever, and treatment delays between the two groups. Differences between the two groups in durations of fever, antibiotic usage, and hospitalization were analyzed by the Wilcoxon rank sum test. The Log-rank test was used to compare the durations of ANC less than 500/cumm in the two groups.

RESULTS

Incidences of sepsis in Group A and Group B were 35.7% (5/14) and 40.4% (23/57), respectively. Gram-positive, gram-negative, and polymicrobial septicemia comprised 14.3% (4/28), 75% (21/28), and 10.7% (3/28), respectively. Neutropenic fever developed in 9 courses (64.3%, 9/14) in Group A and 21 courses (36.8%, 21/57) in Group B. One patient died of sepsis and the other patient died of pneumonia in Group A and no patient died in Group B. The incidences of mortality were 14.3% (2/14) in group A and 0% (0/57) in group B. The patient who died of sepsis, a 3-year-old boy with relapsed ALL, had received two courses of HD C/T. G-CSF was used in the first course and not used in the second course. The patient who died of pneumonia, a 7-year-old girl with relapsed AML, received 3 courses of HD C/T with G-CSF and 6 courses of HD C/T without G-CSF. Chemotherapies were postponed in 10 courses in Group A (83.3%, 10/12, deleted two mortal courses) and in 16 courses in Group B (28%, 16/57), respectively. Reasons for treatment delay were neutropenia or infection. There were no significant differences in the incidences of sepsis and neutropenic fever between the two groups ($P = 1$ and 0.06, respectively), although there was a trend for lower incidence of neutropenic fever in Group B. Both mortality and treatment delay were significantly lower in Group B ($P = 0.037$ and $P = 0.0006$, respectively). The average number of days required to use antibiotics was 17 in Group A and 8 in Group B. Group B had significantly fewer days of antibiotic treatment ($P = 0.0006$). The total numbers of febrile days and hospital stay were also shorter in Group B (average febrile days 10 in Group A vs. 5 in Group B, $P = 0.0023$; average hospital stay days 37 in Group A vs. 17 in Group B, $P = 0.0001$). The time to ANC recovery above 500/cumm was significantly shorter in Group B (the average 21 days in Group A and 11 in Group B, $P = 0.0001$).

TABLE II. Characteristics of the Patients Receiving Granulocyte Colony-Stimulating Factor*

No.	Leukemia	Status	Chemotherapy	No. of HD C/T for reinduction	No. of HD C/T for consolidation
1	ALL	2nd relapse	HD Ara-C + VP-16	1	
2	ALL	3rd CR	HD Ara-C + VP-16		2
3	ALL	1st relapse	HD Ara-C + Mito	1	
4	ALL	2nd CR	HD Ara-C + Mito		1
		2nd CR	HD Ara-C + VP-16		2
		2nd CR	HD Ara-C + I		2
		2nd CR	HD Ara-C + A		2
5[a]	AML	1st relapse	HD Ara-C + VP-16	1	
		2nd CR	HD Ara-C + VP-16		4
		2nd CR	HD Ara-C + Mito		2
		2nd relapse	HD Ara-C + VP-16	1	
		3rd CR	HD Ara-C + VP-16		1
		3rd CR	HD Ara-C + I		2
		3rd CR	HD Ara-C + A		2
		3rd relapse	HD Ara-C + I	1	
6	AML	2nd CR	HD Ara-C + VP-16		4
7	AML	1st CR	HD Ara-C + VP-16		1
		1st CR	HD Ara-C + I		1
8–12	AML	1st CR	HD Ara-C + VP-16		1
		1st CR	HD Ara-C + I		1
		1st CR	HD Ara-C + A		1
		1st CR	HD Ara-C + Mito		1

*ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CR: in complete remission; HD C/T: high-dose cytarabine containing chemotherapy; HD: high-dose; Ara-C: cytarabine; Mito: mitoxantrone; I: idarubicin; A: asparaginase.
[a]Patient no. 5 is a case of AML transformed from chronic myeloid leukemia.

TABLE III. Characteristics of the Patients Participated in Both Groups*

No.	Leukemia	Status	Chemotherapy	With or without G-CSF	No. of HD C/T for induction or reinduction	No. of HD C/T for consolidation
1	ALL	Refractory	HD Ara-C + Mito	Without	1	
		1st CR	HD Ara-C + VP-16	Without		1
		1st CR	HD Ara-C + VP-16	With		1
2	ALL	2nd relapse	HD Ara-C + VP-16	Without	1	
		3rd CR	HD Ara-C + VP-16	Without		1
		3rd CR	HD Ara-C + VP-16	With		1
3[a]	ALL	3rd relapse	HD Ara-C + Mito	With	1	
		3rd relapse	HD Ara-C + Mito	Without	1	
4[a]	AML	2nd relapse	HD Ara-C + VP-16	Without	2	
		3rd CR	HD Ara-C + VP-16	With		3
		3rd relapse	HD Ara-C + VP-16	Without	2	
		3rd relapse	HD Ara-C + Mito	Without	2	

*ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CR: in complete remission; HD C/T: high-dose cytarabine containing chemotherapy; HD: high-dose; Ara-C: cytarabine; Mito: mitoxantrone; G-CSF: granulocyte colony-stimulating factor.
[a]Expired patient.

DISCUSSION

The recent studies suggest that HD C/T is responsible for an improved outcome in patients with refractory or relapsed ALL and AML [14–16]. According to retrospective analysis, Ara-C 3 g/m^2/dose does not seem superior to 1 g/m^2/dose due to its severe toxicity resulting in more early death. Therefore, we used 1 g/m^2/dose of Ara-C. These intensive regimens result in increased myelosuppression-related morbidity and mortality [1,2,5,17,18]. Spadea et al. reported that profound myelosuppression resulted in fever and infection in almost 100% of patients. Their patients, who were of poor-risk AML, received a single course of regimen including mitoxantrone (6 mg/m^2/day for 6 days), etoposide (80 mg/m^2/day for 6 days), and Ara-C (1 gm/m^2/day for 6 days) [5]. Kantarjian et al. described that 92% their patients who received HD C/T required hospitalization due to fever [2]. Without the use of colony-stimulating factors in high-dose chemotherapy, the mortality rate varies from 5 to 17% and infectious complications arose in more than 50% [17].

G-CSF has proved useful for the recovery of severe

neutropenia after intensive chemotherapy or BMT [19–23]. This effect results in reducing the probability and severity of infectious complications and contributes to shorter durations of fever, intravenous antibiotic use, and hospital stay. In addition, prolonged interruptions of chemotherapy administration are less frequent; this may in turn increase cure rate. Because of the good effect of G-CSF, intensive regimens can have widespread use [20,22,23].

Although group B had an advantage in this study due to inclusion of 6 patients with de novo AML who received 22 courses with G-CSF, the use of G-CSF as an adjunct to HD C/T in patients with acute leukemia overall was associated with favorable results. A cost analysis was not done in this study; however, it was apparent that benefit of cost was obtained by reduction of the durations of antibiotic usage and hospitalization.

CONCLUSIONS

G-CSF prophylactically administered following HD C/T significantly reduces mortality, the durations of fever, antibiotic administration, and hospitalization, and allows for tighter adherence to the chemotherapy schedule. A randomized and well-controlled study is warranted to further clarify the role of G-CSF as an adjunct in HD C/T.

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